

Inositol phosphatase SHIP1 is a primary target of miR-155.

Journal:	Proc Natl Acad Sci U S A
Publication Year:	2009
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PubMed link:	19359473
Funding Grants:	CIRM Type I Comprehensive Training Program

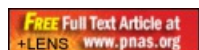
Public Summary:

MicroRNA-155 (miR-155) has emerged as a critical regulator of immune cell development, function, and disease. However, the mechanistic basis for its impact on the hematopoietic system remains largely unresolved. Because miRNAs function by repressing specific mRNAs through direct 3'UTR interactions, we have searched for targets of miR-155 implicated in the regulation of hematopoiesis. In the present study, we identify Src homology-2 domain-containing inositol 5-phosphatase 1 (SHIP1) as a direct target of miR-155, and, using gain and loss of function approaches, show that miR-155 represses SHIP1 through direct 3'UTR interactions that have been highly conserved throughout evolution. Repression of endogenous SHIP1 by miR-155 occurred following sustained over-expression of miR-155 in hematopoietic cells both in vitro and in vivo, and resulted in increased activation of the kinase Akt during the cellular response to LPS. Furthermore, SHIP1 was also repressed by physiologically regulated miR-155, which was observed in LPS-treated WT versus miR-155(-/-) primary macrophages. In mice, specific knockdown of SHIP1 in the hematopoietic system following retroviral delivery of a miR-155-formatted siRNA against SHIP1 resulted in a myeloproliferative disorder, with striking similarities to that observed in miR-155-expressing mice. Our study unveils a molecular link between miR-155 and SHIP1 and provides evidence that repression of SHIP1 is an important component of miR-155 biology.

Scientific Abstract:

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